THE CLAIMS

We claim:

1. A method of reducing, treating or preventing drug-mediated respiratory depression in an animal, incident to the administration to said animal of a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a delta receptor agonist compound.

2. A method according to claim 1, wherein the delta agonist also exhibits mu receptor agonist character.

3. A method according to claim 1, wherein said delta receptor agonist is administered with a separate mu receptor agonist compound.

4. A method according to claim 1, wherein the delta agonist is selected from the group consisting of:

(-)-4-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

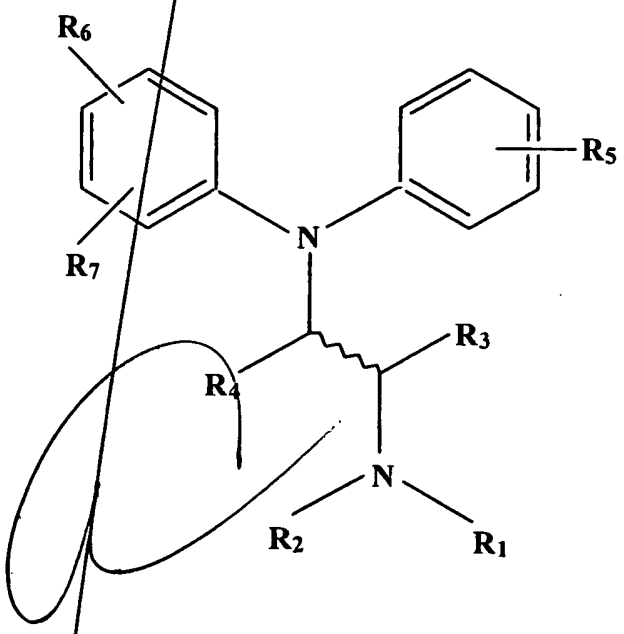
(-)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide,

deltorphin I;

deltorphin II; and

[D-Pen^2,D-Pen^5]-enkephalin.

5. A method according to claim 1, wherein said delta agonist comprises a compound of the formula:



in which,

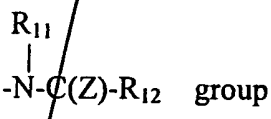
R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, or R_4 is oxygen forming with the carbon atom to which is attached a C=O group;

R_5 is hydrogen, hydroxy, C_{1-3} alkoxy, thiol or alkylthio;

R_6 is phenyl, halogen, NH_2 or a para or meta -C(Z)-R_8 group, in which Z is oxygen or sulphur;

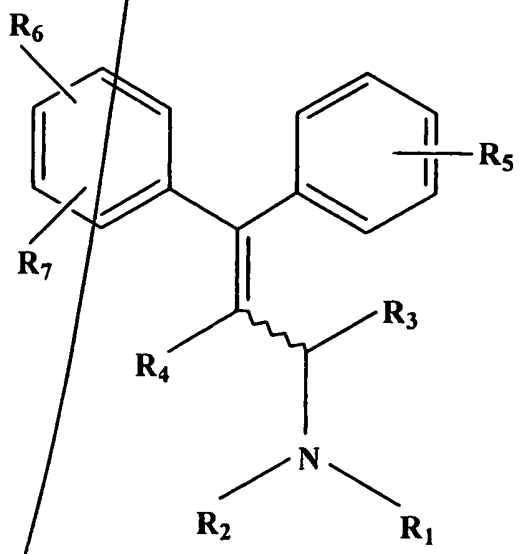
R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a para or metal  group

in which R_{11} and R_{12} which may the same or different are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen.

6. A method according to claim 1, wherein said delta agonist comprises a compound of the formula:



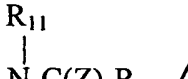
in which,

R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl;

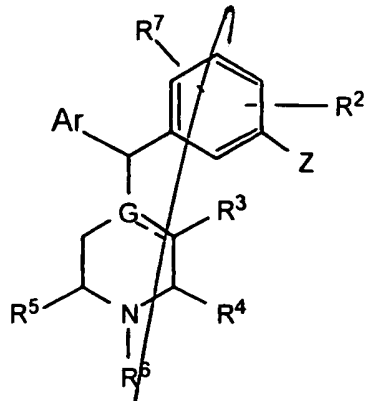
R_5 is hydroxy, C_{1-6} alkoxy, thiol or alkylthio;

R_6 is a -C(Z)-Rg group, in which Z is oxygen or sulphur, R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a  group

in which R_{11} and R_{12} have the same meaning as R_9 and R_{10} or together form an optionally substituted heterocyclic ring and Z is as defined above, and R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen.

7. A method of reducing, treating or preventing drug-mediated respiratory depression in an animal, comprising administering to the animal an effective amount of a compound of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1,

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;

alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;

C_2-C_4 cyanoalkyl;

C_2-C_4 hydroxyalkyl;

aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.

8. A method according to claim 7, wherein Ar is a 6-member carbocyclic aromatic (benzene) ring and R^1 is hydrogen.

9. A method according to claim 7, wherein Y is a carboxamide of the formula $CONR^9R^{10}$.

10. A method according to claim 9, wherein R^9 and R^{10} together form a ring of five or six atoms, thereby forming a pyrrolidinyl or piperidino ring.

11. A method according to claim 9, wherein R^9 and R^{10} are the same or different and are each independently selected from hydrogen, C_1 alkyl and C_2 alkyl.

12. A method according to claim 8, wherein Y is hydrogen.

13. A method according to claim 8, wherein Y is a sulfone of the formula SO_2R^8, and R^8 is C_1-C_6 alkyl.

14. A method according to claim 8 wherein G is N, R^7 and R^2 are each hydrogen, and Z is hydroxyl.

15. A method according to claim 8, wherein R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl.

16. A method according to claim 9, wherein R^6 is selected from the group consisting of hydrogen, methyl, propyl, allyl and butenyl.

17. A method according to claim 14, wherein R^3, R^4 and R^5 are hydrogen or methyl, where the total number of methyl groups is one or two.

18. A method according to claim 7, wherein R^3 and R^5 are both methyl, and R^4 is hydrogen.

19. A method according to claim 7 wherein the compound is selected from the group consisting of:

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(-)-4-((αR)-α-((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

4-((αR)-α-(2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

N,N-diethyl-4-((αR)-3-hydroxy-α-((2R,5R)-2,5-dimethyl-1-piperazinyl)benzyl)benzamide;

4-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-methyl-benzamide;

3-((αR)- α-((2S, 5S)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-N,N-diethyl-4-((αR*)-3-hydroxy-α-((2R*,5S*)-2,4,5-trimethyl-1-piperazinyl)benzyl)-benzamide;

(+)-4-((αS)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

3-((αR)-4-(piperidinocarbonyl)- α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

3-((αR)-4-(1-pyrrolidinylcarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

(±)-3-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-4-(methylsulfonyl)benzyl)-phenol;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfon-amide; or

(-)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide,

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-4-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxbenzyl)benzamide;

(±)-4-((αR*)-α-((2R*,5S*)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

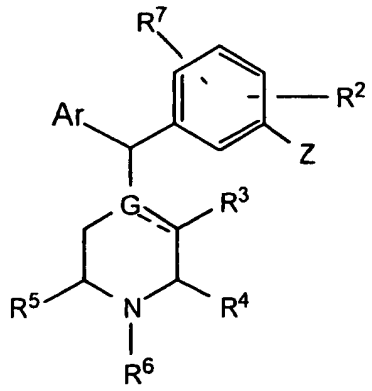
(±)-cis-4-(α-(4-allyl-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

cis-4-(α-(3,5-dimethyl-4-(methylallyl)-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

and pharmaceutically acceptable salts thereof.

20. A method according to claim 19, wherein the compound is (-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide or a pharmaceutically acceptable salt thereof.

21. A method for screening opioid respiratory depression-suppressing compounds, comprising conducting activity reversal assays of a candidate respiratory depression-suppressing compound in receptor tissue to determine if the candidate respiratory depression-suppressing compound transductionally mediates a respiratory depression effect in the receptor tissue, in response to a respiration-depressing composition, wherein said activity reversal assays are conducted comparatively, in the absence and in the presence of an anti-suppression compound of the formula



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1,

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:
hydroxyl, and esters thereof;
hydroxymethyl, and esters thereof; and
amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:
hydrogen;
C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
C_3-C_6 cycloalkyl;
arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;
alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;
C_2-C_4 cyanoalkyl;
C_2-C_4 hydroxyalkyl;
aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and
$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof,

to determine if the activity of the candidate compound is substantially reversed at the tissue site by the presence of the anti-suppression compound of formula (I), thereby indicating the candidate respiratory depression-suppressing compound as possessing potential bioefficacy for supressing respiratory depression effects incident to the use of other therapeutic agents.

22. A method according to claim 21, wherein the anti-suppression compound of formula (I) is selected from the group consisting of:

(-)-4-((αS)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(-)-4-((αS)-α-((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide; and

cis-4-(α-(4-((Z)-2-butenyl)-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide; and

acceptable salts thereof.

23. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression, muscle rigidity, and/or nausea/vomiting as an unwanted side effect thereof; and

(2) a delta receptor agonist.

24. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression, muscle rigidity, and/or nausea/vomiting as an unwanted side effect thereof; and

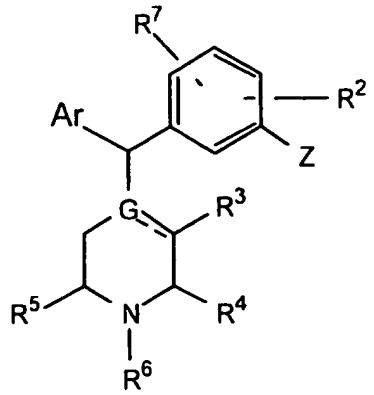
(2) a delta receptor agonist selected from the group consisting of:

I. [D-Pen^2,D-Pen^5]-(enkephalin);

II. deltorphin I;

III. deltorphin II;

IV. delta agonist compounds of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1,

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;
hydroxymethyl, and esters thereof; and
amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

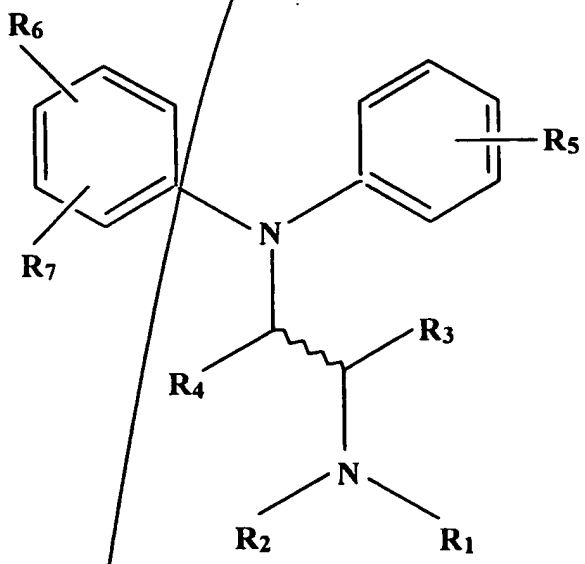
R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:
hydrogen;
C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;
C_3-C_6 cycloalkyl;
arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;
alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;
C_2-C_4 cyanoalkyl;
C_2-C_4 hydroxyalkyl;
aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and
$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof;

V. delta agonist compounds of the formula:



in which,

R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, or R_4 is oxygen forming with the carbon atom to which is attached a C=O group;

R_5 is hydrogen, hydroxy, C_{1-3} alkoxy, thiol or alkylthio;

R_6 is phenyl, halogen, NH_2 or a para or meta -C(Z)-R_8 group, in which Z is oxygen or sulphur;

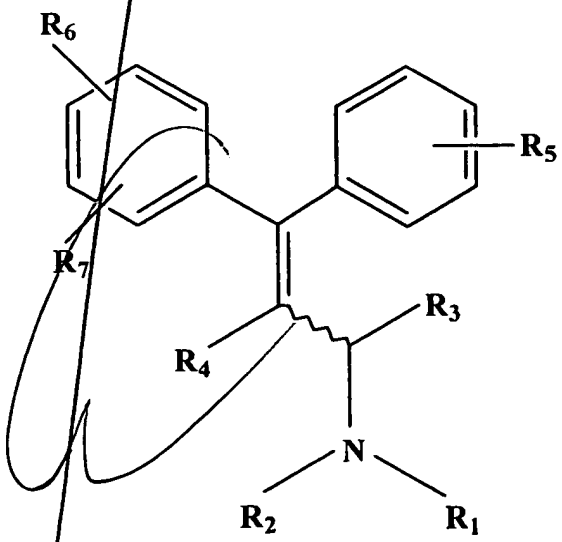
R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a para or metal $-N-C(Z)-R_{12}$ group (R_{11})

in which R_{11} and R_{12} which may the same or different are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen; and

VI. delta agonist compounds of the formula:



in which,

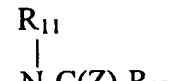
R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl,

aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl;

R_5 is hydroxy, C_{1-6} alkoxy, thiol or alkylthio;

R_6 is a -C(Z)-Rg group, in which Z is oxygen or sulphur, R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a  group

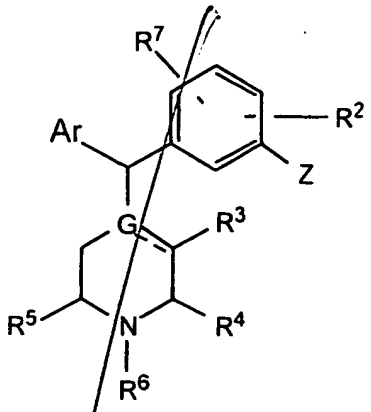
in which R_{11} and R_{12} have the same meaning as R_9 and R_{10} or together form an optionally substituted heterocyclic ring and Z is as defined above, and R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen.

25. A pharmaceutical composition according to claim 24, in a form suitable for injectable or spinal administration.

26. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression; and

(2) an effective amount of a compound for reducing, treating or preventing respiratory depression, of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1,

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;

alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;

C_2-C_4 cyanoalkyl;

C_2-C_4 hydroxyalkyl;

aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.

27. A pharmaceutical composition according to claim 26, wherein Ar is a 6-member carbocyclic aromatic (benzene) ring and R^1 is hydrogen.

28. A pharmaceutical composition according to claim 26, wherein Y is a carboxamide of the formula $CONR^9R^{10}$.

29. A pharmaceutical composition according to claim 26, wherein R^9 and R^{10} together form a ring of five or six atoms, thereby forming a pyrrolidinyl or piperidino ring.

30. A pharmaceutical composition according to claim 26, wherein R^9 and R^{10} are the same or different and are each independently selected from hydrogen, C_1 alkyl and C_2 alkyl.

31. A pharmaceutical composition according to claim 26, wherein Y is hydrogen.

32. A pharmaceutical composition according to claim 26, wherein Y is a sulfone of the formula SO_2R^8 and R^8 is C_1-C_6 alkyl.

33. A pharmaceutical composition according to claim 26, wherein G is N, R^7 and R^2 are each hydrogen, and Z is hydroxyl.

34. A pharmaceutical composition according to claim 26, wherein R^6 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl and C_2-C_6 alkynyl.

35. A pharmaceutical composition according to claim 26, wherein R^3, R^4 and R^5 are hydrogen or methyl, where the total number of methyl groups is one or two.

36. A pharmaceutical composition according to claim 26, wherein R^3 and R^5 are both methyl, and R^4 is hydrogen.

37. A pharmaceutical composition according to claim 26, wherein the compound is selected from the group consisting of:

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(-)-4-((αR)-α-((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

4-((αR)-α-(2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

N,N-diethyl-4-((αR)-3-hydroxy-α-((2R,5R)-2,5-dimethyl-1-piperazinyl)benzyl)benzamide;

4-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-methyl-benzamide;

3-((αR)- α-((2S, 5S)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-N,N-diethyl-4-((αR*)-3-hydroxy-α-((2R*,5S*)-2,4,5-trimethyl-1-piperazinyl)benzyl)-benzamide;

(+)-4-((αS)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

3-((αR)-4-(piperidinocarbonyl)- α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

3-((αR)-4-(1-pyrrolidinylcarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

(±)-3-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-4-(methylsulfonyl)benzyl)-phenol;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfon-amide; or

(-)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide,

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-4-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxbenzyl)benzamide;

(±)-4-((αR*)-α-((2R*,5S*)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(±)-cis-4-(α-(4-allyl-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

cis-4-(α-(3,5-dimethyl-4-(methylallyl)-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

and pharmaceutically acceptable salts thereof.

38. A pharmaceutical composition according to claim 37, wherein the compound is (-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide or a pharmaceutically acceptable salt thereof.

39. A pharmaceutical composition according to claim 26, wherein the bioactive compound comprises an opiate compound.

40. A pharmaceutical composition according to claim 26, wherein the bioactive compound comprises an opiate analgesic compound.

41. A pharmaceutical composition according to claim 26, wherein the bioactive compound comprises a mu opiate compound.

42. A method of treating a patient in need thereof with fentanyl while attenuating fentanyl-induced muscle rigidity and fentanyl-induced respiratory depression, comprising administering to the patient a delta agonist compound in an effective amount to attenuate said fentanyl-induced muscle rigidity and fentanyl-induced respiratory depression.

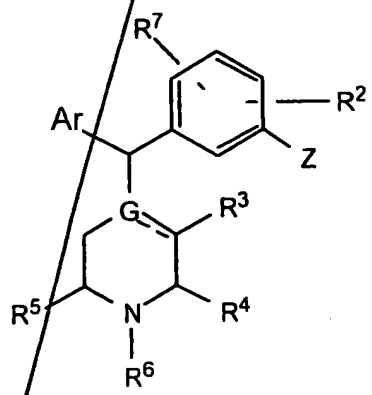
43. A method of treating a patient in need thereof with an opioid receptor therapeutic agent, while attenuating respiratory depression incident to the administration thereof, comprising administering to the patient with said opioid receptor therapeutic agent, a delta agonist compound selected from the group consisting of :

I. [D-Pen^2,D-Pen^5]-(enkephalin);

II. deltorphin I;

III. deltorphin II;

IV. delta agonist compounds of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent R^1,

Y is selected from the group consisting of:

hydrogen;

halogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_1-C_6 haloalkyl;

C_1-C_6 alkoxy;

C_3-C_6 cycloalkoxy;

sulfides of the formula SR^8 where R^8 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, arylalkyl having a C_5-C_{10} aryl moiety and an C_1-C_6 alkyl moiety, or C_5-C_{10} aryl;

sulfoxides of the formula SOR^8 where R^8 is the same as above;

sulfones of the formula SO_2R^8 where R^8 is the same as above;

nitrile;

C_1-C_6 acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where R^8 is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where R^9 and R^{10} may be the same or different, and may be hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 hydroxyalkyl, C_2-C_6 methoxyalkyl, C_3-C_6 cycloalkyl, or C_5-C_{10} aryl, or R^9 and R^{10} together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where R^9 and R^{10} are the same as above, or C_2-C_{30} peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where R^9 and R^{10} are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

R^1 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^2 is hydrogen, halogen, or C_1-C_4 alkyl, C_2-C_4 alkenyl, C_1-C_4 alkynyl;

R^3, R^4 and R^5 may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of R^3, R^4 or R^5 is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of R^3, R^4 and R^5 together may form a bridge of 1 to 3 carbon atoms;

R^6 is selected from the group consisting of:

hydrogen;

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

C_3-C_6 cycloalkyl;

arylalkyl having C_5-C_{10} aryl and C_1-C_6 alkyl moieties;

alkoxyalkyl having C_1-C_4 alkoxy and C_1-C_4 alkyl moieties;

C_2-C_4 cyanoalkyl;

C_2-C_4 hydroxyalkyl;

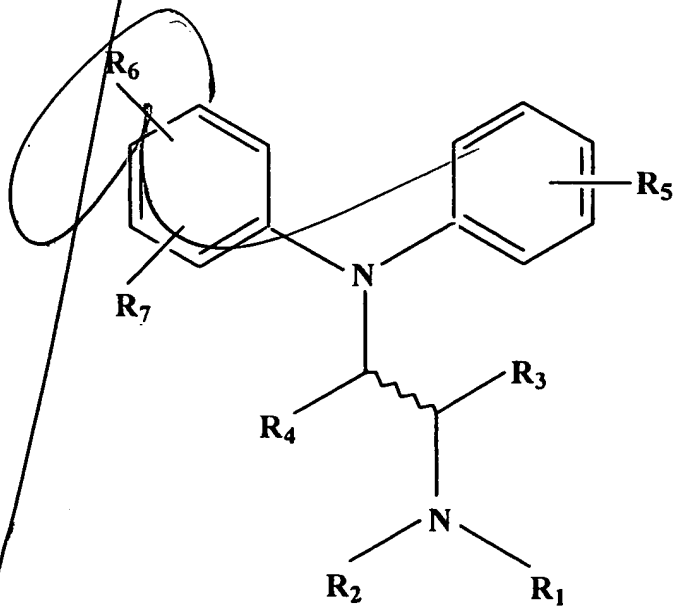
aminocarbonylalkyl having a C_1-C_4 alkyl moiety; and

$R^{12}COR^{13}$, where R^{12} is C_1-C_4 alkylene, and R^{13} is C_1-C_4 alkyl or C_1-C_4 alkoxy; and

R^7 is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof;

V. delta agonist compounds of the formula:



in which,

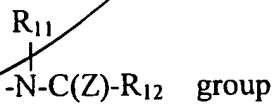
R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, or R_4 is oxygen forming with the carbon atom to which is attached a C=O group;

R_5 is hydrogen, hydroxy, C_{1-3} alkoxy, thiol or alkylthio;

R_6 is phenyl, halogen, NH_2 or a para or meta $-C(Z)-R_8$ group, in which Z is oxygen or sulphur;

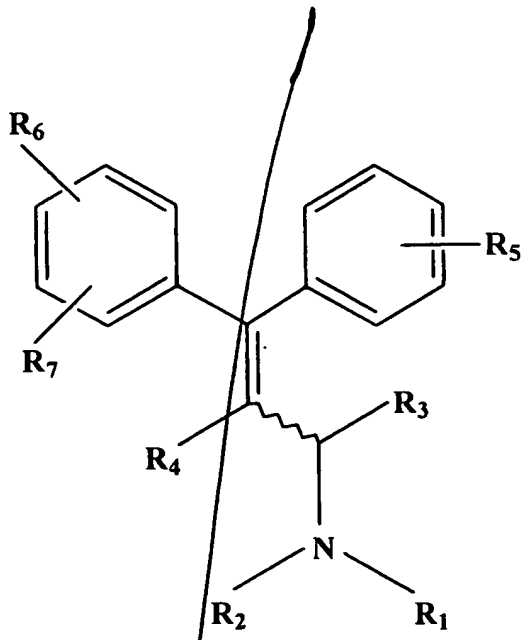
R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a para or meta  group

in which R_{11} and R_{12} which may the same or different are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen; and

VI. delta agonist compounds of the formula:



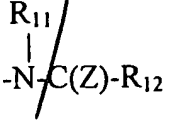
in which,

R_1 and R_2, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkenyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, C_{3-5} alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a C_{3-7} alkyl ring which may be interrupted by oxygen.

R_3 and R_4, which can be the same or different, are each hydrogen, linear or branched C_{1-6} alkyl;

R_5 is hydroxy, C_{1-6} alkoxy, thiol or alkylthio;

R_6 is a -C(Z)-Rg group, in which Z is oxygen or sulphur, R_8 is C_{1-8}-alkyl, C_{1-8}-alkoxy or NR_9R_{10}, wherein R_9 and R_{10}, which may be the same or different, are hydrogen, straight or branched C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{4-6} cycloalkylalkyl, C_{3-6} alkenyl, aryl or aralkyl,

or R_6 is a  group

in which R_{11} and R_{12} have the same meaning as R_9 and R_{10} or together form an optionally substituted heterocyclic ring and Z is as defined above, and R_7 is hydrogen, straight or branched C_{1-8} alkyl or halogen.

45. A method of reducing, treating or preventing drug-mediated respiratory depression in an animal, incident to the administration to said animal of a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a compound selected from the group consisting of:

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfon-amide; and

(-)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide, and

pharmaceutically acceptable salts thereof.

46. A method of reducing, treating or preventing drug-mediated respiratory depression, muscle rigidity, or nausea/vomiting in an animal, incident to the administration to said animal of a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a delta receptor agonist or a mixed delta/mu opioid agonist composition.